UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte STEVEN FINKBEINER

Appeal No. 2007-0859
Application No. 09/922,483
Technology Center 1600

Decided: October 31, 2007

Before DEMETRA J. MILLS, LORA M. GREEN, and NANCY J. LINCK, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

The Appellant appeals the Examiner's final rejection of claims 10-13 and 28-30 for lack of enablement.

We have jurisdiction under 35 U.S.C. § 6(b) (2006).

Representative claim 10 reads as follows:

10. A method of determining whether an agent is capable of modulating the binding interaction between a protein comprising a polyglutamine expansion and a cellular target of said protein, said method comprising:

(a) contacting said protein or a binding fragment or mimetic thereof with:

(i) said agent; and

(ii) an antibody that recognizes a protein comprising a polyglutamine expansion or binding fragment or mimetic thereof, wherein said antibody has greater affinity for said polyglutamine expansion than a 1C2 monoclonal antibody;

(b) detecting the presence of binding complexes comprising said protein and said antibody; and

(c) comparing the results of step (b) with a control;

wherein the ability of an agent to modulate the binding interaction between said protein and said antibody indicates that the ability of said agent to modulate the binding interaction between said protein and a cellular target of said protein.

Cited References

South et al. "Identification of Novel Peptide Antagonists for von Willebrand Factor Binding to the Platelet Glycoprotein Ib Receptor from a Phage Epitope Library, Vol. 73, *Journal of the Intenational Society on Thrombosis and Haemostasis*, pp. 144-150 (1995) (hereinafter South)

Heiser et al. "Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: Implications for Huntington's disease therapy," Vol. 97, No. 12, *Proceeding of the National Academy of Science*, pp. 6739-6744 (2000) (hereinafter Heiser)

Kaji et al. "Peptide Mimics of Monocyte Chemoattractant Protein-1

((MCP-1) with an Antagonistic Activity," *The Journal of Biochemistry*, Vol. 129 No. 4 pp. 577-583 (2001) (hereinafter Kaji)

Grounds of Rejection

Claims 10-13 and 28-30 stand rejected under 35 USC 112, first paragraph for lack of enablement.

We affirm.

DISCUSSION

Background

"Huntington's Disease (HD) is a devastating neurological disease which usually presents in mid adult life . ... HD is associated with expansion of a CAG repeat within the HD gene. ... The HD gene encompasses 67 exons, spans over 200 kb and is associated with two transcripts of 10.3 kb and 13.6 kb, differing with respect to their 3' untranslated regions. ... [T]he HD gene encompasses a highly polymorphic CAG [polyglutamine] repeat which varies in number from 8 to 35 in normal individuals. CAG expansion beyond 36 CAG repeats is seen in persons with HD." (Specification 1-2.)

The Specification, pages 17-18, discloses Appellant found 6 monoclonal antibodies specific for the mutant polyglutamine expansion, designated 1F11E5, 4H7H7, 3A2D3, 4F1B5, 3C4A6, 3B5H10 which differ from a known antibody, 1C2, specific for the polyglutamine repeat in HD by at least one of specificity, affinity and avidity. The Specification further describes binding fragments of the antibodies and binding mimetics which share the binding characteristics of the antibodies for the polyglutamine expansion protein, *e.g.*, mutant huntingtin protein. (Specification 8.)

> The subject antibodies, binding fragments and mimetics thereof ... find use in screening applications designed to identify agents or compounds that are capable of modulating, e.g. inhibiting, the binding

> interaction between the protein to which the antibody binds and a cellular target. For example, the subject antibodies find use in screening assays that identify compounds capable of modulating the interaction between mutant huntingtin protein and its cellular targets. In such assays, the subject antibody is contacted with mutant huntingtin protein in the presence of a candidate modulation agent and any resultant binding complexes between the antibody and the mutant huntingtin protein are detected. The results of the assay are then compared with a control. Those agents which change the amount of binding complexes that are produced upon contact are identified as agents that modulate the binding activity of mutant huntingtin protein and therefore are potential therapeutic agents. Of interest in many embodiments is the identification of agents that inhibit, at least to some extent, the binding of mutant huntingtin protein with its target.

(Specification 11-12.)

Enablement

Claims 10-12, and 28-30 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

The Examiner contends that the "preamble of the claim is directed to identifying compounds capable of modulating the interaction between mutant huntingtin protein and its (cellular) targets. Yet the method steps outlined in the claim will only measure the interaction between mutant huntingtin protein and an antibody." (Answer 3.) Thus, the Examiner argues, that "the specification does not teach a method of screening agents that will interfere with the interaction of mutant huntingtin protein with the normal cellular target of the huntingtin protein" as the "normal cellular target of the hungtingtin protein is not known." (Answer 4.) The Examiner argues that the claimed methods cannot distinguish whether the agent binds to the antibody or the polyglutamine containing protein itself. (Answer 4.) Thus, according to the Examiner, if the agent binds only the antibody it would

not be useful to prevent the binding of the huntingtin protein to the undisclosed and unidentified cellular receptor. (Answer 4.)

Therefore, as we understand it, the Examiner's position appears to be that Appellant has not disclosed in the Specification information about the cellular targets recited in claim 10, i.e., specific information about a cellular receptor or target for mutant huntingtin protein, and has not disclosed agents which interfere with the binding reaction claimed. For these reasons, the Examiner finds enablement is lacking for the claimed subject matter.

Appellant contends that the Examiner has failed to establish a reasonable basis to question enablement. (Br. 8.) In particular, Appellant argues that "[t]he Examiner has apparently misunderstood the claimed invention" and that "[t]he antibodies in the claimed method do not serve to prevent the binding of the polyglutamine expansion-containing protein to its cellular target. Instead, the antibodies serve as surrogates for the cellular target." (Br. 11.) Appellant argues that "those skilled in the art would find it reasonable that a polyglutamine expansion-containing protein binds to an antibody specific for the polyglutamine expansion of the polyglutamine expansion-containing protein in a manner similar to the binding of a cellular target of the polyglutamine expansion-containing protein." (Br. 11.)

Thus, Appellant takes the position that "those skilled in the art would also find it reasonable to use an antibody as a surrogate for the cellular target(s) of a polyglutamine expansion-containing protein in a screening method to identify agents that modulate binding interaction between a polyglutamine expansion-containing protein and a cellular target of the protein." (*Id.*)

Enablement is a question of law, based on underlying findings of fact. *See, e.g., In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138.

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [*Id.* at 737, 8 USPQ2d at 1404.]

"Patent protection is granted in return for an enabling disclosure . . . , not for vague intimations of general ideas that may or may not be workable." *Genentech*, 108 F.3d at 1365, 42 USPQ2d at 1005. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention." *Id.,* 42 USPQ2d at 1005 (emphasis added).

In the present case, the quantity of experimentation necessary to determine whether an agent is capable of modulating the binding interaction between a protein comprising a polyglutamine expansion and a cellular target of the protein

based on the method of claim 10 would be undue. The Specification does not provide any correlation between an antibody that binds a polyglutamine expansion protein and the actual cellular target for the polyglutamine expansion. The Specification does not disclose or characterize any agents which interfere with the claimed binding reaction. The lack of direction or guidance presented in the Specification concerning the cellular target for the polyglutamine expansion and the absence of working examples of compounds which modulate the binding interaction between a protein comprising the polyglutamine expansion and the cellular target is evident upon review of the Specification.

As noted by the Examiner,

> In order for an antibody to be considered a "surrogate receptor" it would have to bind the huntingtin protein at the same location that the undisclosed and unidentified cellular target binds the polyglutamine expansion of the huntingtin protein. The antibody would have to occupy the same location (space) on the huntingtin protein as the cellular target, for the antibody to be a "surrogate" cellular target. Thus, the antibody would have to interfere with the huntingtin protein binding to the cellular target. A compound that interferes with the antibody binding to the polyglutamine expansion protein can act on the antibody alone or the compound can bind to the polyglutamine expansion protein. Only those compounds that bind to the polyglutamine expansion protein may affect the binding of the protein to the cellular target. However, the instantly claimed method cannot determine to which protein (huntingtin or the antibody) the agents bind. Therefore, the claimed method cannot determine if the agent is capable of modulating the interaction between the polyglutarnine expansion protein and the cellular target. Neither the specification nor the art has established that antibody binding to the polyglutamine expansion region of the huntingtin protein occurs in the same region that binds the unknown and undisclosed cellular target.

(Answer 5-6.)

The nature of the invention is such that the art has a high level of unpredictability. The state of the prior art is indicated by Heiser, which evidences that the formation of *insoluble* protein aggregates (fibrillar proteins) plays an important role in the cellular distortions underlying HD and the related glutamine-repeat disorders. (Heiser, col. 1, p. 6739.) Heiser further evidences that antibody 1C2 was known to recognize the conformation of an elongated polyQ tract in *soluble* proteins, but not the array of glutamine residues in insoluble protein aggregates with fibrillar morphology. (Heiser, col. 2, p. 6740.) Heiser further indicates that "the causal relationship between aggregate formation and disease has not been proven," but genetic, neuropathological, and biochemical evidence indicates that the formation of insoluble protein aggregates plays an important role in the cellular distortions underlying HD. (Heiser, col. 1, p. 6739.) Thus, the state of the art as reflected by Heiser, does not recognize or provide information about the function of the mutant huntingtin protein in HD or the nature of the normal cellular target for the mutant huntingtin protein. (Answer 5.) Finally, the claims are broadly drawn to a method of determining whether an agent is capable of modulating the binding interaction between a protein comprising a polyglutamine expansion and a cellular target of said protein. The Specification does not disclose any agent, chemical or protein, capable of modulating the claimed binding interaction. The Specification does not provide guidance as to the nature of the actual cellular target for polyglutamine expansion protein.

According to the Appellant

> [a]ll that claim 10 requires is that the polyglutamine expansion containing protein be contacted with the agent and an antibody that recognizes the polyglutamine expansion of the polyglutamine expansion-containing protein (where the antibody has greater affinity for the polyglutamine expansion than a 1C2 monoclonal antibody); and that the presence of a binding complex between the antibody and

> the polyglutamine expansion-containing protein be detected and compared to a control. The ability of the agent to modulate the binding interaction between the polyglutamine expansion containing protein and the antibody indicates the ability of the agent to modulate binding interaction between the polyglutamine expansion-containing protein and a cellular target of the polyglutamine expansion containing protein. Thus, the antibody in the claimed method serves as a surrogate for the cellular target(s) of the polyglutamine expansion-containing protein.

(Br. 7.)

Appellant further argues that

> [t]he instant specification provides ample description of antibodies to be used in a subject method; as well as ample description as to how to determine whether an agent modulated binding of an antibody to a polyglutamine expansion of a polyglutamine expansion-containing protein. The specification describes antibodies, and binding fragments and mimetics of such antibodies, which specifically bind to polyglutamine expansion-containing proteins, such as mutant huntingtin protein. Specification, page 3, lines 23-25; page 4, line 20 to page 6, line 26; and page 8, line 25 to page 9, line 11; and page 18, line 28-page 19, line 1. The specification describes how to determine whether an agent modulated binding of an antibody to a polyglutamine expansion of a polyglutamine expansion-containing protein. Specification, page 11, line 24 to page 12, line 30. Given the description in the specification, those skilled in the art could readily practice the method as claimed without undue experimentation.

(Br. 7.)

Appellant concludes that

> [t]he person skilled in the art would find it reasonable that cellular target(s) for polyglutamine expansion-containing protein include proteins. The person skilled in the art would find it reasonable that a polyglutamine expansion containing protein binds to an antibody specific for the polyglutamine expansion of the

> polyglutamine expansion-containing protein in a manner similar to the binding of the cellular target of the polyglutamine expansion-containing protein.

(Br. 7.)

We are not persuaded by these arguments. What is critically missing from the portions of the disclosure pointed to by Appellant is the nature of the natural cellular target of the mutant huntingtin protein. The Specification does not provide any relationship between the six antibodies obtained by Appellant which are specific for the mutant huntingtin protein and any cellular target for mutant huntingtin protein.

In further support of this position regarding enablement, Appellant puts for the Declaration under 37 C.F.R. 1.132 of Ross Stein. As explained in the Declaration of Stein, "the antibody used in the assay has a specific binding site for a toxic conformation of polyglutamine." Declaration ¶4. The Declarant speculates that "[t]he binding site on the antibody might have structural features and binding properties for polyglutamine that are similar to binding sites on the cellular proteins that mediate the toxic effects of polyglutamine. Small drug-like molecules that bind to the site on the antibody might also bind to the cellular proteins." Declaration, ¶4. Moreover, the Declarant states that the assay was a key component on a grant applicatioin submitted to the National Institute of Neurological Disorders and Stoke (NINDS), and that the comments of a NINDS panel "were strongly supportive of the science of the grant, including this assay. Declaration ¶5.

We are not persuaded by the speculative conclusions drawn in the Declaration. The Declaration speculates that the antibody binding site might have structural features and binding properties for polyglutamine that are similar to

binding sites on the cellular proteins that mediate the toxic effects of polyglutamine, but this remains a hypothesis, and there is no evidence that both the antibody and the cellular target share a similar conformation. We also cannot evaluate the statements made in paragraph 5 of the Declaration, as neither the grant application, nor the comments of the NINDS panel appear to accompany the Declaration.

Appellant also relies on Kaji and South as teaching that it is known in the art to use antibodies as surrogates for a cellular target in a manner similar to that claimed. (Br. 10-11.) Appellant argues that Kaji describes the screening of a phage display library with monoclonal antibodies that inhibit the chemotactic activity of monocyte chemoattractant protein (MCP-1). (Br. 10.) The method identified two peptides that bound to THP-1 cells (which are responsive to MCP-1), and it was determined that the binding was competitively inhibited by MCP-1. *Id.* From this Kaji concluded that the peptides mimic the MCP-1 binding domain that is recognized by the MCP-1 receptor. (Kaji, col. 2, p. 577.) Appellant argues Kaji used the antibodies as a surrogate for the MCP-1 receptor and found that peptides that bound the antibody also bound the receptor CC chemokine receptor 2 (CCR2). (Br. 10; Kaji, col. 2, p. 577.) However, Kaji could draw no evidentiary conclusions that its phage clones shared binding properties with the CCR2 receptor. Kaji describes that the binding region of MCP-1 to its receptor CCR2 had been identified by mutational analysis. (Kaji, col. 1, p. 582.) Kaji found a sequence with low sequence similarity to the binding region of MCP-1 in its synthetic peptides C25 and C27. (*Id.*) Kaji stated that, "it is conceivable that both phage clones may bind to the structure of CCR2 shared with other MCP-1 receptors. The precise binding specificity of these phage clones remains to be studied." (Kaji, col. 1, p. 582.)

Appellant argues South screened a phage display library for inhibitors of the von Willebrand factor (vWF) platelet Glycoprotein Ib (GPIb) interaction. (Br. 11.) The phage display library was screened with a monoclonal antibody that recognizes the GPIb binding domain of vWF. (South, Abstract.) In particular, South screened an epitope library with a monoclonal antibody that neutralizes the biological activity of a GPIb receptor/ligand interaction. (South, col. 2, p. 144.) South used a well characterized antibody to von Willebrand factor that disrupts vWF binding to the platelet GPIb receptor. (South, col. 2, p. 144.) The Examiner indicates that the "critical difference between the cited paper [South] and the instant specification is that in the South et al. paper the authors actually knew that the antibody binds to the GPIb domain that recognizes the vWF." (Final Rejection 3.) In the present case, unlike South, the natural target for the polyglutamine repeat is unknown, and it is unverified that the antibodies share the same binding specificity with a known receptor or target. Thus we do not find either Kaji or South to be convincing evidence that one of ordinary skill in the art would have been enabled to practice the claimed method without undue experimentation, or that either of these publications evidence that, in every case, an antibody to a protein acts as a surrogate for the cellular target of the protein.

A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion in question is true. *Herman v. Huddleston*, 459 U.S. 375, 390 (1983). In the present case we find that the preponderance of the evidence supports the Examiner's position that the claimed invention is not enabled—primarily because the nature of the cellular target of mutant huntingtin protein is not known in the prior art or described in the Specification. Therefore the rejection of the claims for lack of enablement is affirmed.

CONCLUSION

The rejection of claims 10-13 and 28-30 under 35 U.S.C. § 112, first paragraph, for lack of enablement are affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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